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Mechanism of Isoniazid-Induced Hepatotoxicity: Academic Case.

Camilo García Espada[1], Kevin Oswaldo Urbano[2], Alejandro Rincón Castillo[3], Aura Lizeth Bastidas Mora[4], Daniela Gutiérrez Payares[5], Mayra Alejandra Sánchez Rengifo[6], Jhan Sebastian Saavedra Torres[7], Ylanith Camila Lugo Sánchez[8]

[1,2,3,4,5]M.D- Departamento de Ginecología Clínica; Clínica Nuestra Señora de Los Remedios- Valle del Cauca- Universidad Libre seccional Cali, Colombia.

[6]M.D- Universidad Libre Seccional Cali. Departamento de Medicina Interna, Clínica Nuestra Señora de Los Remedios - Cali, Colombia.

[7]MD, M. Sc en Cuidados paliativos- Universidad de Nebrija (Madrid- España). Residente de Medicina Familiar – Departamento de Clínicas Médicas- Pontificia Universidad Javeriana de Cali, Colombia.

[8]M.D- Fundación Universitaria San Martin sede Cali, Clínica Nuestra Señora de Los Remedios- Valle del Cauca- Colombia.

ABSTRACT

Isoniazid is used to treat or prophylaxis tuberculosis; However, its use may be associated with adverse liver reactions. Clinically overt hepatitis occurs in 0.5%-1% of patients receiving isoniazid as monotherapy. This clinical case reported allows the academy to always verify and monitor liver function in those who have medications that cause damage to liver cells.

KEYWORD'S: biomarker, hepatotoxicity, immune mediated, reactive metabolite, tolerance.

ARTICLE DETAILS

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LEARNING POINTS

1. Due to its high efficacy, isoniazid (INH) remains the drug of choice for treatment of latent tuberculosis (TB) despite the fact that it can cause liver failure.
2. Although drug-induced liver injury (DILI) caused by different drugs is somewhat different, the clinical characteristics of INH-induced liver injury are fairly typical for idiosyncratic DILI and include malaise, fatigue, nausea and vomiting.
3. The incidence of INH-induced liver injury appears to be higher in patients with the slow acetylator phenotype.
4. This suggests that the higher incidence of liver injury in slow acetylators, and in particular those cases of liver injury that appear to have a immune-mediated phenotype, may be due to higher blood concentrations of INH rather than acetyl hydrazine (AcHz). Other known risk factors for INH-induced liver injury include increased age.

INTRODUCTION: DRUG-INDUCED LIVER INJURY (DILI)

Drug-induced liver injury (DILI) is an adverse reaction to drugs or other xenobiotics that occurs either as a predictable event when an individual is exposed to toxic doses of some compounds or as an unpredictable event with many drugs in common use (1). Drugs can be harmful to the liver in susceptible individuals owing to genetic and environmental risk factors (1,2). These risk factors modify hepatic metabolism and excretion of the DILI-causative agent leading to cellular stress, cell death, activation of an adaptive immune response and a failure to adapt, with progression to overt liver injury (2,3).

INTRODUCTION: ACUTE HEPATITIS

Acute hepatitis is an inflammatory process that results in the death of liver cells, and that can be initiated by viral infection, or in this case, by exposure to toxic substances (2,3). Prescription and nonprescription drugs are common initiators of acute liver injury, and can be divided into predictable, dose-related toxicity (e.g., acetaminophen) and unpredictable, idiosyncratic reactions, as with isoniazid. Isoniazid is a rare but important cause of acute hepatitis, and in susceptible individuals may be due to genetic predisposition and certain drug metabolism pathways that create toxic intermediates (3,4). Synergistic drug reactions have also been implicated in acute liver failure.

Discontinuation of the offending agent is typically followed by recovery of normal liver function (4,5).

PATIENT PRESENTATION

A 28-year-old male, who recently migrated from the Philippines, underwent a tuberculin skin test at the clinic with a positive result. Chest x-ray did not show active tuberculosis, and the subject denied symptoms of this infection, including weight loss, cough, or night sweats. Daily dosing with isoniazid was recommended for the next nine months to prevent future illness.

Two weeks after starting therapy, the patient reported progressive fatigue, intermittent bouts of nausea, and pain in the abdomen. He also noted darkening of the urine and light-colored stools. The patient's wife noticed changes in the color of his eyes and jaundice was noted, attributing the increase in serum bilirubin and aminotransferases. Isoniazid was discontinued and symptoms reduced, with normalization of liver enzymes.

RESULTS

The latency period between exposure to the medication and the development of DILI ranges from 5 to 90 days. Upon removal of the suspect drug, aminotransferases should decrease by at least 50% over the next 8 days (3,5). Re-exposure to the medication as diagnostic confirmation may be considered unethical, except when there is no other therapeutic option. Reported cases of inadvertent rechallenge confirm that a given drug is hepatotoxic (4,6). Elevated aminotransferases or alkaline phosphatase alone, without hyperbilirubinemia or jaundice, is considered mild disease. Jaundice or hyperbilirubinemia >2 mg/dL indicates severe disease, as in the case presented. If there is jaundice associated with INR >1.5, encephalopathy, or ascites, the risk of mortality is up to 21% in the case of DILI due to anti-tuberculosis drugs (5,7).

DISCUSSION

Histologic findings in acute hepatitis include focal degeneration and necrosis of liver cells, portal inflammation with mononuclear cell infiltrate, bile duct prominence, and cholestasis. Less frequently, acute hepatitis may result in bridging necrosis. The normal lobular structure is mostly restored during the recovery phase (2,3).

Jaundice of the skin and sclera on physical examination suggest hyperbilirubinemia due to intrahepatic cholestasis caused by acute liver injury (4,5). As a result, there is inappropriate excretion of conjugated bilirubin into the bile, which explains the appearance of clay-colored stools. Likewise, there is extrusion of conjugated bilirubin from hepatocytes into the bloodstream, and the kidneys excrete its water-soluble metabolites, which darkens the urine. These changes in stool and urine often precede clinically obvious jaundice (3,4). Yellow skin pigmentation reflects the accumulation of water-insoluble bilirubin metabolites and is usually not seen on examination until serum bilirubin rises above 2.5 mg/dL (1-5).

CONCLUSION

DILI is a diagnosis of exclusion; other more frequent causes of liver injury such as infectious or autoimmune hepatitis, NASH, biliary obstruction, vascular lesions, liver neoplasms, Wilson's disease or hemochromatosis must always be ruled out (6,7).

FOOTNOTES

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Ethical consideration: Informed consent was obtained for the publication of clinical data of the patient.

Narrative synthesis: A systematic review of the cases with the rare mechanism of isoniazid-induced hepatotoxicity was able to suggest core and supportive clinical features and narratively summarized data on available treatment approaches.

From evidence to decision: Several authors have described various important reasons to publish case reports/series in mechanism of isoniazid-induced hepatotoxicity.

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